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U S Department of Commerce Patent and Trademark Office

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
PI/5-20691/A/PCT

U S. APPLICATION NO. (If known, see 37 CFR 1 5)
09/091333

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
EP/96/05564	12 December 1996 (12.12.96)	21 December 1995 (21.12.95)

TITLE OF INVENTION
PROCESS FOR THE PREPARATION OF 2-CHLORO-5-CHLOROMETHYL-THIAZOLE

APPLICANT(S) FOR DO/EO/US
O'SULLIVAN ET AL.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau. (See Form PCT/IB/308)
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C.371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An executed Declaration and Power of Attorney (original or copy) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included.

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information: unsigned Declaration and Power of Attorney

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
	EP/96/05564	PI/5-20691/A/PCT

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):

		CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO	$930	
International preliminary examination fee paid to USPTO (37 CFR 1.482)	$720	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).	$790	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.	$1,070	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).	$98	

ENTER APPROPRIATE BASIC FEE AMOUNT = $ 930

Surcharge of **$130** for furnishing the oath of declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)). $

CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE			
Total claims	52	- 20 =	32	X	$	22	$ 704
Independent claims	2	- 3 =	0	X	$	82	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)				+	$	270	$

TOTAL OF ABOVE CALCULATIONS = $ 1,634

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28). $

SUBTOTAL = $ 1,634

Processing fee of **$130** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). + $

TOTAL NATIONAL FEE = $ 1,634

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40** per property + $

TOTAL FEES ENCLOSED = $ 1,634

Amount to be: refunded $

charged $

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge Deposit Account No. 19-0134 in the amount of $1,634 to cover the above fees. A duplicate copy of this form is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0134.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to the address associated with Customer No. 001095, which is currently:

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CASE PI/5-20691/A/PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF

O'SULLIVAN ET AL.

INTERNATIONAL APPLICATION NO: EP/96/05564

FILED: 12 DECEMBER 1996

U.S. APPLICATION NO: Not Yet Known

35 USC §371 DATE: Herewith

FOR: PROCESS FOR THE PREPARATION OF 2-CHLORO-5-CHLOROMETHYL-THIAZOLE

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to substantive examination, kindly amend the application as follows:

IN THE SPECIFICATION

On page 1, before the first paragraph, please insert the following:

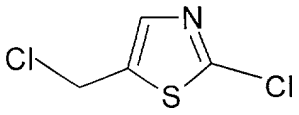
-- This is a 371 of PCT/EP/96/05489, December 7, 1996. ---

Page 4, line 14, after "Javelle water", insert -- (NaHClO) --.

IN THE CLAIMS

Cancel, without prejudice, claims 8, 11, 14, 17, 21, 25, 28, 32, 36, 39, 43, 47, 53, 57, 65 and 68.

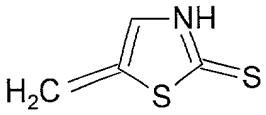
1. (Amended) A process for preparing [the] a compound of the formula



I,

which comprises

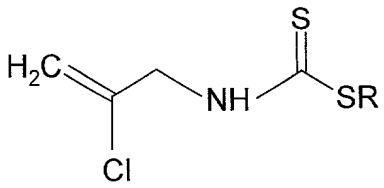
a) reacting a [the known] compound of the formula



II,

in free form or in salt form, with a chlorinating agent, or

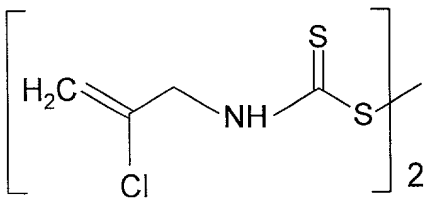
(b) reacting a compound of the formula



III,

[which is known or can be prepared by methods known per se and] in which R is C_1-C_6alkyl, C_3-C_6cycloalkyl or an unsubstituted or mono- to pentasubstituted aryl or aryl-C_1-C_4alkyl group, where the substituents are selected from the group consisting of halogen and C_1-C_4alkyl, with a chlorinating agent, or

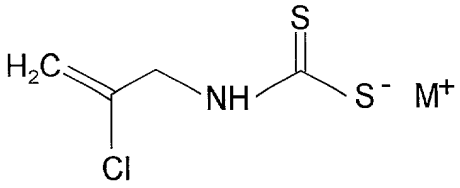
c) reacting [the] a compound of the formula



IV

with a chlorinating agent, or

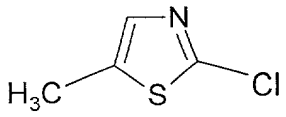
d) reacting a compound of the formula



V,

[which is known or can be prepared by methods known per se and] in which M^+ is an alkali metal ion, one equivalent of an alkaline earth metal ion or is a nonalkylated ammonium ion or an ammonium ion which is alkylated with from one to four identical or different alkyl radicals, [and is preferably a potassium ion or, in particular, a sodium ion,] with a chlorinating agent, or

e) reacting [the] a compound of the formula



VI,

[which is known,] in the presence or absence of a free-radical catalyst, with a chlorinating agent, or

f1) first reacting the compound of [the] formula II or the compound 2-mercapto-5-methyl-thiazole, in each case in free form or in salt form, with a chlorinating agent, and

f2) subjecting the compound of [the] formula VI [which is obtainable in this way] to further reaction, with or without isolating it, with a chlorinating agent in accordance with variant e), or

g) subjecting a compound of [the] formula V either

g1.1) first to treatment with a base and

g1.2) the compound of the formula II [thus obtainable], in free form or in salt form, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2), or

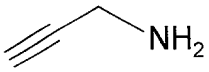
g2.1) first to reaction with a compound of the formula RX[, which is known or can be prepared by methods known per se and] in which R is as defined for the formula III and X is a leaving group, and

g2.2) the compound of [the] formula III [thus obtainable], with or without isolating it, to further reaction with a chlorinating agent in accordance with variant b), or

g3.1) first of all to reaction with an oxidizing agent, optionally in the presence [or absence] of a base, and

g3.2) the compound of the formula IV [thus obtainable], with or without isolating it, to further reaction with a chlorinating agent in accordance with variant c), or

h1) reacting the compound of [the] formula

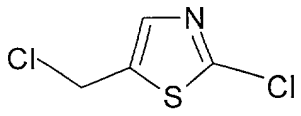


VII,

[which is known,] first of all with carbon disulfide, optionally in the presence [or absence] of a base, and

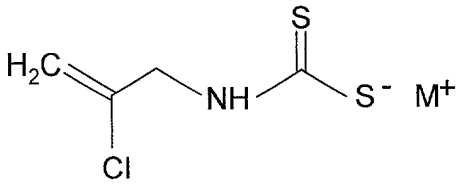
h2) further reacting the compound of the formula II [thus obtainable], in free form or in salt form, with or without isolating it, with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2).

61. (Amended) [A] The process according to claim 1 for the preparation of the compound of [the] formula



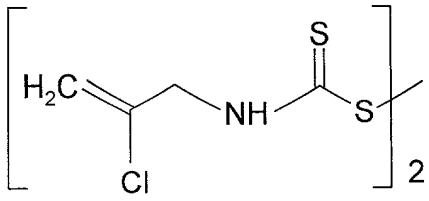
I,

which comprises reacting a compound of [the] formula



V,

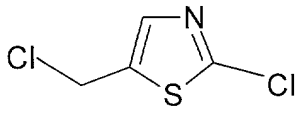
in which M^+ is as defined in claim 1, with an oxidizing agent, optionally in the presence [or absence] of a base, and further reacting the compound thus obtainable, of the formula



IV

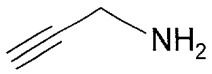
with or without isolating it, with a chlorinating agent.

62. (Amended) A process according to claim 1 for the preparation of a compound of the formula



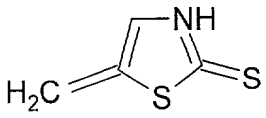
I,

which comprises reacting the compound of the formula



VII,

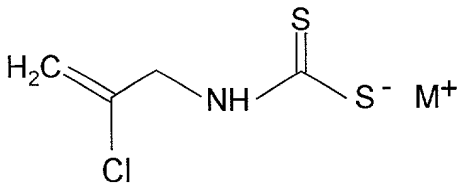
with carbon disulfide, optionally in the presence [or absence] of a base, and further reacting the compound thus obtainable, of the formula



II,

in free form or in salt form and with or without isolating it, with a chlorinating agent.

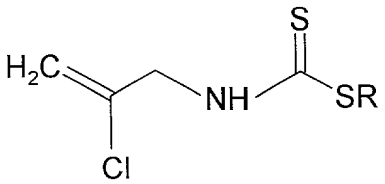
64. (Amended) A process for the preparation of the compound according to claim 63[, of the formula IV,] which comprises reacting a compound of the formula



V,

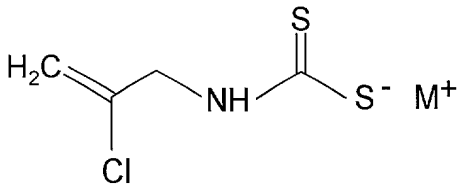
in which M^+ is an alkali metal ion, one equivalent of an alkaline earth metal ion or is a nonalkylated ammonium ion or an ammonium ion which is alkylated with from one to four identical or different alkyl radicals [as defined in claim 1], with an oxidizing agent, optionally in the presence [or absence] of a base.

67. (Amended) A process for the preparation of a compound [according to claim 66,] of the formula [III],



III,

which comprises reacting a compound of the formula



V,

in which M^+ is as defined in claim 1, with a compound of the formula RX, in which R is as defined in claim 1 for the formula III and X is a leaving group.

REMARKS

Applicants have added into the specification, page 4, the chemical structure equivalent -- (NaHClO) -- to further define the known term "Javelle water".

Applicants have cancelled, without prejudice, claims 8, 11, 14, 17, 21, 25, 28, 32, 36, 39, 43, 47, 53, 57, 65 and 68 in order to reduce claim fees. Applicants reserve the right to file claims to the subject matter of those cancelled claims in this application, or other applications claiming the benefits hereof.

Applicants have also amended claims 1, 61-62, 64 and 67 to render the language more clear and concise. No new matter has been added by these editorial changes.

Early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

Michael P. Morris

Michael P. Morris
Attorney for Applicants
Reg. No. 34,513

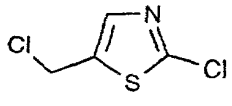
Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6937

MPM:mjl

Date: JUN 16 1998

Process for the preparation of 2-chloro-5-chloromethyl-thiazole

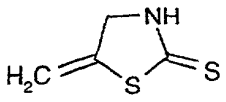
The invention relates to a process for preparing the known compound of the formula



I,

which comprises

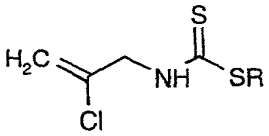
a) reacting the known compound of the formula



II,

in free form or in salt form, with a chlorinating agent, or

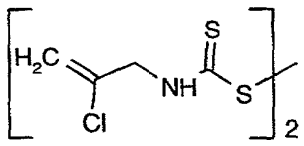
b) reacting a compound of the formula



III,

which is known or can be prepared by methods known per se and in which R is C_1-C_6alkyl, C_3-C_6cycloalkyl or an unsubstituted or mono- to pentasubstituted aryl or aryl-C_1-C_4alkyl group, where the substituents are selected from the group consisting of halogen and C_1-C_4alkyl, with a chlorinating agent, or

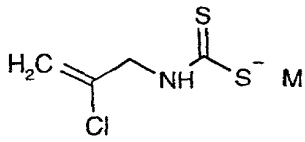
c) reacting the compound of the formula



IV

with a chlorinating agent, or

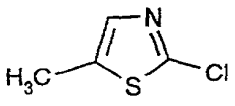
d) reacting a compound of the formula



V,

which is known or can be prepared by methods known per se and in which M^+ is an alkali metal ion, one equivalent of an alkaline earth metal ion or is a nonalkylated ammonium ion or an ammonium ion which is alkylated with from one to four identical or different alkyl radicals, and is preferably a potassium ion or, in particular, a sodium ion, with a chlorinating agent, or

e) reacting the compound of the formula



VI,

which is known, in the presence or absence of a free-radical catalyst, with a chlorinating agent, or

f1) first reacting the compound of the formula II or the compound 2-mercapto-5-methyl-thiazole, in each case in free form or in salt form, with a chlorinating agent, and

f2) subjecting the compound of the formula VI which is obtainable in this way to further reaction, with or without isolating it, with a chlorinating agent in accordance with variant e), or

g) subjecting a compound of the formula V either

g1.1) first to treatment with a base and

g1.2) the compound of the formula II thus obtainable, in free form or in salt form, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2), or

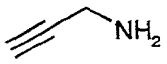
g2.1) first to reaction with a compound of the formula RX, which is known or can be prepared by methods known per se and in which R is as defined for the formula III and X is a leaving group, and

g2.2) the compound of the formula III thus obtainable, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant b), or

g3.1) first of all to reaction with an oxidizing agent, in the presence or absence of a base, and

g3.2) the compound of the formula IV thus obtainable, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant c), or

h1) reacting the compound of the formula



VII,

which is known, first of all with carbon disulfide, in the presence or absence of a base, and

h2) further reacting the compound of the formula II thus obtainable, in free form or in salt form, with or without isolating it, with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2);

to the compounds of the formulae III and IV, which are employed in this process as intermediates; and to the use of, and a process for the preparation of, the compounds of the formulae III and IV.

2-Chloro-5-chloromethylthiazole I is an important intermediate in the preparation of compounds having a pesticidal action, as are described, for example, in EP-A-0 192 060.

Unless defined otherwise, the general terms used above and below have the following meanings.

Halogen - both as a group on its own and as a structural element of other groups and compounds, such as of haloalkyl and halocyclopropyl - is fluorine, chlorine, bromine or iodine, especially fluorine, chlorine or bromine, in particular fluorine or chlorine, and most especially chlorine.

Compounds and groups containing carbon include, unless defined otherwise, in each case from 1 up to and including 6, preferably from 1 up to and including 3, and in particular 1 or 2, carbon atoms.

Cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably cyclopropyl.

Alkyl - both as a group per se and as a structural element of other groups and compounds, such as of phenylalkyl and haloalkyl - is (always taking into account the particular number of

carbon atoms in the relevant group or compound) either straight-chain, i.e. methyl, ethyl, propyl, butyl, pentyl or hexyl, or branched, e.g. isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl or isohexyl.

Aryl is phenyl oder naphthyl, especially phenyl.

Depending on requirements, the reactions described above and below are carried out in the presence or absence of an appropriate solvent or diluent or mixture thereof, with cooling, at room temperature or heating, for example in a temperature range from about -80°C to the boiling temperature of the reaction medium, preferably from about -60°C to about +200°C, in a closed vessel under atmospheric, elevated or reduced pressure, under an inert gas atmosphere and/or under hydrogen-free conditions. Particularly advantageous reaction conditions are described below and can be inferred in particular from the Preparation Examples.

Variant a):

Examples of suitable chlorinating agents are elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride or mixtures of two or more of these compounds, preferably elemental chlorine, sulfuryl chloride or a mixture of these two compounds, particularly preferably sulfuryl chloride.

The reactants can be reacted with one another without adding a solvent or diluent. However, the addition of a solvent or diluent or mixture thereof may also be advantageous, its amount not being critical. Examples of such solvents or diluents are: water; alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, ethylene glycol or glycerol, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, such as benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene or tetrachloroethene; ethers, such as diethyl ether, dipropyl ether, diisopropyl ether, dibutyl ether, tert-butyl methyl ether, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol dimethyl ether, dimethoxydiethyl ether, tetrahydrofuran or dioxane; amides, such as N,N-dimethylformamide, N,N-diethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or hexamethylphosphoramide; nitriles, such as acetonitrile or propionitrile; and sulfoxides, such as dimethyl sulfoxide. If reaction is carried out in the

presence of an organic acid, then it is also possible for acids employed in excess, for example strong organic carboxylic acids, such as unsubstituted or substituted - for example by halogen - C_1-C_4alkanecarboxylic acids, examples being formic acid, acetic acid or propionic acid, to be used as solvent or diluent. The reaction is preferably carried out in the presence of a halogenated hydrocarbon, especially in dichloromethane.

Reaction takes place advantageously in a temperature range from about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant a) a compound II is reacted at from 0 to 40°, preferably from 10 to 15°, with a chlorinating agent, preferably sulfuryl chloride.

Reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

The yields obtained are generally good. It is possible to attain a yield of about 70 % of the theoretical yield.

Preferred conditions for the reaction are described in Examples H1 to H3.

Variant b):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant b), a compound III is reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H4.

Variant c):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant c), a compound IV is reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H5.

Variant d):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent

or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Variant e):

Examples of suitable free-radical catalysts are azobis(isobutyronitrile) or, in particular, dibenzoyl peroxide.

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant e), a compound VI is reacted at 10 to 120°, preferably 80°, with a chlorinating agent, preferably N-chlorosuccinimide.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 100 hours is preferred, especially from 12 to 72 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H6.

Variant f1/f2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +80°C, preferably from about -10°C to about +40°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant f1/f2), a compound II is initially reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride, to give a compound of the formula VI which then, preferably after it has been isolated, is subjected to further reaction with a further chlorinating agent, preferably N-chlorosuccinimide.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 100 hours is preferred, especially from 1 to 72 hours, preferably from 12 to 72 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

2-Mercapto-5-methyl-thiazole, which can be used also in its tautomeric form (2-thioxo compound), can be obtained, for example, by acid treatment of the compound of the formula II.

Preferred conditions for the reactions are described in Examples H6, H7 and H9.

Variant g1.1):

Examples of suitable bases for facilitating the reaction are alkali metal or alkaline earth metal hydroxides, hydrides, amides, alkanolates, acetates, carbonates, dialkylamides or alkylsilylamides, alkylamines, alkylenediamines, nonalkylated or N-alkylated, saturated or unsaturated cycloalkylamines, basic heterocycles, ammonium hydroxides and carbocyclic amines. Specific examples are sodium hydroxide, hydride, amide, methanolate, acetate and carbonate, potassium tert-butanolate, hydroxide, carbonate and hydride, lithium

diisopropylamide, potassium bis(trimethylsilyl)amide, calcium hydride, triethylamine, diisopropylethylamine, triethylenediamine, cyclohexylamine, N-cyclohexyl-N,N-dimethylamine, N,N-diethylaniline, pyridine, 4-(N,N-dimethylamino)pyridine, quinuclidine, N-methylmorpholine, benzyltrimethylammonium hydroxide and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU).

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +80°C, preferably from about -10°C to about +40°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 100 hours is preferred, especially from 12 to 72 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Variant g1.2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant g1.2), a compound II is reacted at 0 to 40°, preferably 10 to 15°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Examples H1 to H3, H6, H7 and H9.

Variant g2.1):

Suitable leaving groups X are, for example, hydroxyl, C_1-C_8alkoxy, halo-C_1-C_8alkoxy, C_1-C_8alkanoyloxy, mercapto, C_1-C_8alkylthio, halo-C_1-C_8alkylthio, C_1-C_8alkanesulfonyloxy, halo-C_1-C_8alkanesulfonyloxy, benzenesulfonyloxy, toluenesulfonyloxy and halogen, preferably toluenesulfonyloxy, trifluoromethanesulfonyloxy and halogn, especially halogen.

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Variant g2.2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant g2.2), a compound III is reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H4.

Variant g3.1):

Examples of suitable oxidizing agents are air, nitrogen monoxide, elemental halogens, alkali metal chlorates, inorganic peroxides, for example hydrogen peroxide, or sodium perborate, organic peroxides, for example benzoyl peroxide, or dimethyl sulfoxide, preferably elemental halogens or hydrogen peroxide, especially iodine.

Suitable bases for facilitating the reaction are, for example, of the type indicated under variant g1.1).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant g3.1), a compound V is reacted at -10 to 40°, preferably 0°, with an oxidizing agent, preferably iodine.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H8.

Variant g3.2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant g3.2), a compound IV is reacted at -10 to 40°, preferably 0°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Example H5.

Variant h1):

Examples of suitable bases for facilitating the reaction are those indicated under variant g1.1).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 1 to 24 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Variante h2):

Examples of suitable chlorinating agents are those indicated under variant a).

The reactants can be reacted with one another as they are, i.e. without the addition of a solvent or diluent, for example in the melt. However, in most cases the addition of a solvent or diluent or mixture thereof is advantageous. Examples of suitable solvents and diluents are those indicated under variant a).

Reaction takes place advantageously in a temperature range of about -20°C to about +180°C, preferably from about 0°C to about +80°C, and in many cases in the range between room temperature and the reflux temperature of the reaction mixture.

In a preferred embodiment of variant h2), a compound II is reacted at 0 to 40°, preferably 10 to 15°, with a chlorinating agent, preferably sulfuryl chloride.

The reaction takes place preferably at atmospheric pressure.

The reaction time is not critical; a reaction period of from 0.1 to 48 hours is preferred, especially from 0.5 to 4 hours.

The product is isolated by conventional methods, for example filtration, crystallization, distillation or chromatography, or by any appropriate combination of these methods.

Preferred conditions for the reaction are described in Examples H1 to H3, H6, H7 and H9.

The invention likewise provides starting materials and intermediates which are novel and which are used in accordance with the invention to prepare compound I, a process for their preparation, and their use as starting materials and intermediates for preparing the compound I; this pertains in particular to the compounds III and IV.

The invention likewise provides a process for the preparation of the compounds III and IV. The compound III can be prepared, for example, as described under variant g2.1). The compound IV can be prepared, for example, as described under variant g3.1).

The invention likewise provides for the use of the compound III or IV as an intermediate in the novel process for the preparation of the compound I.

The invention additionally provides starting materials and intermediates, in each case in free form or in salt form if applicable, which are novel and which are used in accordance with the invention for preparing compounds II, III, IV and VI and/or their salts, and to a process for their preparation, and for their use as starting materials and intermediates for preparing compounds II, III, IV and VI.

The compounds II, V, VI and VII are known or, where novel, can be prepared in analogy to known compounds.

The invention relates to all those process embodiments in which the starting material is a compound obtainable as an initial product or intermediate at any stage of the process and in which all or some of the missing steps are carried out or in which a starting material is used in the form of a derivative or salt and/or its racemates or enantiomers or, in particular, is formed under the reaction conditions.

The invention relates in particular to the processes described in Examples H1 to H9.

The examples which follow serve to illustrate the invention. They do not restrict the invention. Temperatures are given in degrees Celsius.

Examples

Example H1: 2-Chloro-5-chloromethylthiazole from 5-methylenethiazolidine-2-thione (compound II)

4 g of chlorine gas are passed at 10-15°C into a solution of 100 ml of acetic acid and 7 ml of water. Subsequently, at the same temperature, 9.2 g of 5-methylenethiazolidine-2-thione, 12 ml of 30 % sodium hydroxide solution, 28 ml of water and 21 g of chlorine gas are metered in over the course of 2-3 hours. Then 100 ml of water are added to this reaction mixture, and extraction is carried out three times with 30 ml of toluene. The organic phase is dried over sodium sulfate and concentrated in vacuo at 45°C to give the title compound in a yield of 56 % (melting point: 35°C).

Example H2: 2-Chloro-5-chloromethylthiazole from 5-methylenethiazolidine-2-thione (compound II)

1.31 g of 5-methylenethiazolidine-2-thione are added in portions at 0°C, with stirring, to a solution of 5.4 g of sulfuryl chloride in 8 ml of dichloromethane and 0.72 ml of water. The reaction mixture is subsequently stirred at room temperature for 1 hour. The mixture is then adjusted to a pH of 2 with 30 % sodium hydroxide solution, and the organic phase is separated off, dried over sodium sulfate and concentrated in vacuo to give the title compound in a yield of 70 % (melting point: 35°C).

Example H3: 2-Chloro-5-chloromethylthiazole from 5-methylenethiazolidine-2-thione (compound II)

1 ml of water at -5°C and then, at the same temperature over the course of 5 minutes, 1.4 g of 5-methylenethiazolidine-2-thione in five portions are added to a mixture of 13 ml of dichloromethane and 10 g of sulfuryl chloride. The reaction mixture is then diluted with 20 ml of water and 33 ml of dichloromethane, it is neutralized with about 24 ml of 30 % sodium hydroxide solution, and the organic phase is separated off. The aqueous phase is subjected to extraction with 27 ml of dichloromethane, and the combined extracts are dried over sodium sulfate and concentrated in vacuo at 35°C, to give the title compound in a yield of 31 % (melting point: 35°C).

Example H4: 2-Chloro-5-chloromethylthiazole from benzyl 2-chloro-2-propenyldithio-carbamate (compound III, R=benzyl)

358 mg of sulfuryl chloride are slowly added dropwise with stirring at 0°C to a solution of 341 mg of benzyl 2-chloro-2-propenyldithiocarbamate in 0.3 ml of dichloromethane. After 18 hours the reaction mixture is concentrated in vacuo at room temperature, the residue is subjected to extraction with hexane, and the organic phase is dried over sodium sulfate and concentrated in vacuo to give the title compound (melting point: 35°C).

Example H5: 2-Chloro-5-chloromethylthiazole from compound IV

283 mg of sulfuryl chloride are slowly added dropwise with stirring at 0°C to a solution of 135 mg of the compound IV in 0.2 ml of dichloromethane. The reaction mixture is stirred at room temperature for 18 hours and subjected to extraction with hexane, and the organic phase is dried over sodium sulfate and concentrated in vacuo to give the title compound (melting point: 35°C).

Example H6: 2-Chloro-5-chloromethylthiazole from 2-chloro-5-methylthiazole (compound VI)

5 mg of dibenzoyl peroxide in portions and then 155 mg of N-chlorosuccinimide are added at room temperature and with stirring to a solution of 124 mg of 2-chloro-5-methylthiazole in 4 ml of carbon tetrachloride. The reaction mixture is boiled under reflux for 64 hours, then a further 5 mg of dibenzoyl peroxide and 155 mg of N-chlorosuccinimide are added, and boiling is resumed for 8 hours. After cooling to room temperature, the suspension is filtered and the residue is washed with carbon tetrachloride. The organic phase is then concentrated in vacuo and the residue is purified by chromatography on silica gel with ethyl acetate/hexane (1:9), to give the title compound (melting point: 35°C).

Example H7: 2-Chloro-5-methylthiazole (compound VI) from 5-methylenethiazolidine-2-thione (compound II)

1.31 g of 5-methylenethiazolidine-2-thione are added in portions with stirring and at 0°C to a solution of 5.4 g of sulfuryl chloride in 8 ml of dichloromethane and 0.72 ml of water. The reaction mixture is subsequently stirred at room temperature for 1 hour and then adjusted to a pH of 2 using 30 % sodium hydroxide solution, and the organic phase is separated off, washed a number of times with water, dried over sodium sulfate and concentrated by evaporation, to give 2-chloro-5-methylthiazole with a boiling point of 174°C.

Example H8: Compound IV from sodium N-(2-chloro-2-propenyl)dithiocarbamate (compound V, M = sodium)

3.81 g of carbon disulfide are added with stirring and at 0°C to a solution of 4.58 g of 2-chloroallylamine in 25 ml of 2 N sodium hydroxide solution. A solution of 6.35 g of iodine and 4.32 g of potassium iodide in a little water is added to the solution of sodium N-(2-chloro-2-propenyl)dithiocarbamate obtainable as described in the first sentence of this example. The crude, oily product is separated off and is purified by chromatography on silica gel using ethyl acetate/hexane (1:10 to 1:1), to give the compound IV.

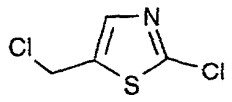
Example H9: 2-Chloro-5-methyl-thiazole (compound VI) from 2-mercapto-5-methyl-thiazole

1.35 g of 2-mercapto-5-methyl-thiazole are added in portions, with stirring and at 0°, to a solution of 5.8 g of sulfuryl chloride in 9 ml of dichloromethane and 720 mg of water. The reaction mixture is subsequently stirred at room temperature for 1 hour and then adjusted to a pH of 2 using aqueous sodium hydroxide solution (30%). The organic phase is separated

off, dried over sodium sulfate and concentrated by evaporation, to give 1.99 g of 2-chloro-5-methyl-thiazole with a boiling point of 174°.

WHAT IS CLAIMED IS:

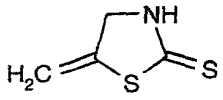
1. A process for preparing the compound of the formula



I,

which comprises

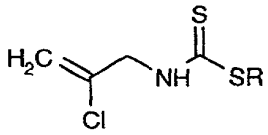
a) reacting the known compound of the formula



II,

in free form or in salt form, with a chlorinating agent, or

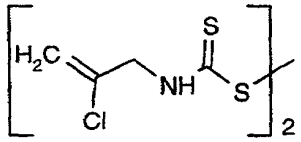
b) reacting a compound of the formula



III,

which is known or can be prepared by methods known per se and in which R is C_1-C_6alkyl, C_3-C_6cycloalkyl or an unsubstituted or mono- to pentasubstituted aryl or aryl-C_1-C_4alkyl group, where the substituents are selected from the group consisting of halogen and C_1-C_4alkyl, with a chlorinating agent, or

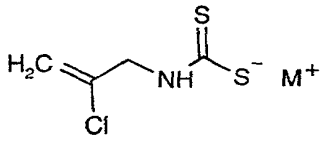
c) reacting the compound of the formula



IV

with a chlorinating agent, or

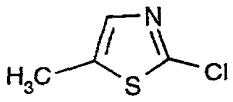
d) reacting a compound of the formula



V,

which is known or can be prepared by methods known per se and in which M^+ is an alkali metal ion, one equivalent of an alkaline earth metal ion or is a nonalkylated ammonium ion or an ammonium ion which is alkylated with from one to four identical or different alkyl radicals, and is preferably a potassium ion or, in particular, a sodium ion, with a chlorinating agent, or

e) reacting the compound of the formula



VI,

which is known, in the presence or absence of a free-radical catalyst, with a chlorinating agent, or

f1) first reacting the compound of the formula II or the compound 2-mercapto-5-methyl-thiazole, in each case in free form or in salt form, with a chlorinating agent, and

f2) subjecting the compound of the formula VI which is obtainable in this way to further reaction, with or without isolating it, with a chlorinating agent in accordance with variant e), or

g) subjecting a compound of the formula V either

g1.1) first to treatment with a base and

g1.2) the compound of the formula II thus obtainable, in free form or in salt form, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2), or

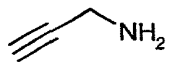
g2.1) first to reaction with a compound of the formula RX, which is known or can be prepared by methods known per se and in which R is as defined for the formula III and X is a leaving group, and

g2.2) the compound of the formula III thus obtainable, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant b), or

g3.1) first of all to reaction with an oxidizing agent, in the presence or absence of a base, and

g3.2) the compound of the formula IV thus obtainable, with or without isolating it, to further reaction with a chlorinating agent in accordance with variant c), or

h1) reacting the compound of the formula

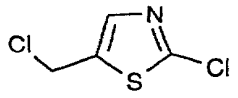


VII,

which is known, first of all with carbon disulfide, in the presence or absence of a base, and

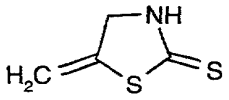
h2) further reacting the compound of the formula II thus obtainable, in free form or in salt form, with or without isolating it, with a chlorinating agent in accordance with variant a) or in accordance with variant f1/f2).

2. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting the compound of the formula



II,

in free form or in salt form, with a chlorinating agent.

3. A process according to claim 2, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

4. A process according to claim 3, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, sulfuryl chloride and a mixture of these two compounds.

5. A process according to claim 4, wherein the chlorinating agent is sulfuryl chloride.

6. A process according to claim 2, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

7. A process according to claim 6, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

8. A process according to claim 7, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

9. A process according to claim 8, wherein the solvent is a mixture of water and dichloromethane.

10. A process according to claim 9, wherein the weight ratio of dichloromethane to water is from about 5 to about 50.

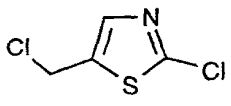
11. A process according to claim 10, wherein the weight ratio of dichloromethane to water is about 10 to about 30.

12. A process according to claim 2, wherein the reaction is carried out at from about -10°C to about +40°C.

13. A process according to claim 2, wherein the reaction period is from about 0.1 to about 4 hours.

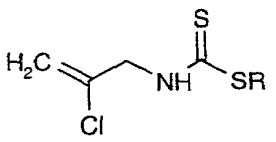
14. A process according to claim 13, wherein the reaction period is from about 0.5 to about 1.5 hours.

15. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting a compound of the formula



III,

in which R is as defined in claim 1, with a chlorinating agent.

16. A process according to claim 15, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

17. A process according to claim 16, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, sulfuryl chloride and a mixture of these two compounds.

18. A process according to claim 17, wherein the chlorinating agent is sulfuryl chloride.

19. A process according to claim 15, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

20. A process according to claim 19, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

21. A process according to claim 20, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

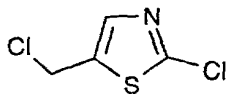
22. A process according to claim 21, wherein the solvent is dichloromethane.

23. A process according to claim 15, wherein the reaction is carried out at from about -10°C to about +40°C.

24. A process according to claim 15, wherein the reaction period is from about 1 to about 48 hours.

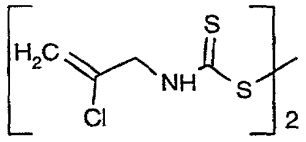
25. A process according to claim 24, wherein the reaction period is from about 12 to about 24 hours.

26. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting a compound of the formula



IV

with a chlorinating agent.

27. A process according to claim 26, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

28. A process according to claim 27, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, sulfuryl chloride and a mixture of these two compounds.

29. A process according to claim 28, wherein the chlorinating agent is sulfuryl chloride.

30. A process according to claim 26, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

31. A process according to claim 30, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

32. A process according to claim 31, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

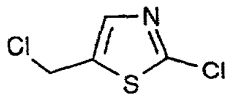
33. A process according to claim 32, wherein the solvent is dichloromethane.

34. A process according to claim 26, wherein the reaction is carried out at from about -10°C to about +40°C.

35. A process according to claim 26, wherein the reaction period is from about 1 to about 48 hours.

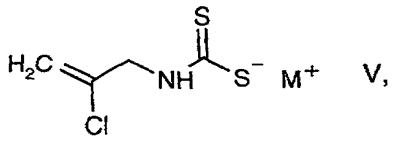
36. A process according to claim 35, wherein the reaction period is from about 12 to about 24 hours.

37. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting a compound of the formula



V,

in which M^+ is as defined in claim 1, with a chlorinating agent.

38. A process according to claim 37, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

39. A process according to claim 38, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, sulfuryl chloride and a mixture of these two compounds.

40. A process according to claim 39, wherein the chlorinating agent is sulfuryl chloride.

41. A process according to claim 37, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

42. A process according to claim 41, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether,

hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

43. A process according to claim 42, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

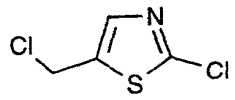
44. A process according to claim 43, wherein the solvent is dichloromethane.

45. A process according to claim 37, wherein the reaction is carried out at from about -10°C to about +40°C.

46. A process according to claim 37, wherein the reaction period is from about 1 to about 48 hours.

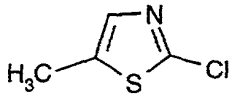
47. A process according to claim 46, wherein the reaction period is from about 12 to about 24 hours.

48. A process according to claim 1 for preparing the compound of the formula



I,

which comprises reacting the compound of the formula



VI,

with a chlorinating agent.

49. A process according to claim 48, wherein the chlorinating agent is selected from the group consisting of elemental chlorine, Javelle water, N-chlorosuccinimide, phosphorus trichloride, phosphorus pentachloride, sulfuryl chloride, thionyl chloride and mixtures of two or more of these compounds.

50. A process according to claim 49, wherein the chlorinating agent is N-chlorosuccinimide.

51. A process according to claim 48, wherein the solvent is selected from the group consisting of water, strong organic carboxylic acids, aromatic, aliphatic and alicyclic hydrocarbons and halogenated hydrocarbons, and mixtures of these solvents.

52. A process according to claim 51, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, propionic acid, benzene, toluene, xylene, mesitylene, tetralin, chlorobenzene, dichlorobenzene, bromobenzene, petroleum ether, hexane, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, dichloroethane, trichloroethene and tetrachloroethene, and mixtures of these solvents.

53. A process according to claim 52, wherein the solvent is selected from the group consisting of water, formic acid, acetic acid, dichloromethane, trichloromethane, tetrachloromethane and dichloroethane, and mixtures of these solvents.

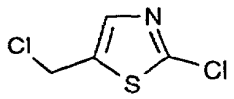
54. A process according to claim 53, wherein the solvent is tetrachloromethane.

55. A process according to claim 48, wherein the reaction is carried out at from about 20°C to about +80°C.

56. A process according to claim 48, wherein the reaction period is from about 1 to about 120 hours.

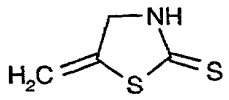
57. A process according to claim 56, wherein the reaction period is from about 48 to about 96 hours.

58. A process according to claim 1 for the preparation of the compound of the formula



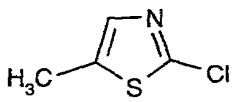
I,

which comprises first reacting the compound of the formula



II

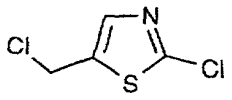
or the compound 2-mercapto-5-methyl-thiazole, in each case in free form or in salt form, with a chlorinating agent and further reacting the compound thus obtainable, of the formula



VI,

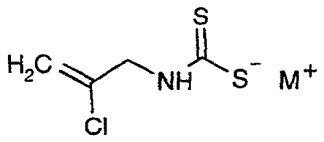
with or without isolating it, with a chlorinating agent.

59. A process according to claim 1 for the preparation of the compound of the formula



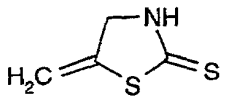
I,

which comprises treating a compound of the formula



V,

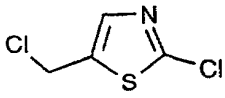
in which M^+ is as defined in claim 1, with a base and further reacting the compound thus obtainable, of the formula



II,

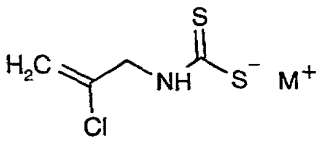
in free form or in salt form and with or without isolating it, with a chlorinating agent.

60. A process according to claim 1 for the preparation of the compound of the formula



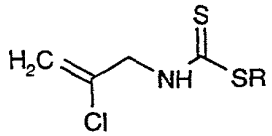
I,

which comprises reacting a compound of the formula



V,

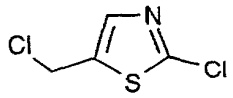
in which M^+ is as defined in claim 1, with a compound of the formula RX, in which R is as defined in claim 1 for the formula III and X is a leaving group, and further reacting the compound thus obtainable, of the formula



III,

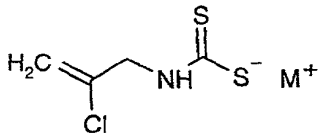
in which R is as defined in claim 1, with or without isolating it, with a chlorinating agent.

61. A process according to claim 1 for the preparation of the compound of the formula



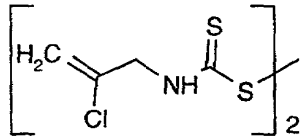
I,

which comprises reacting a compound of the formula



V,

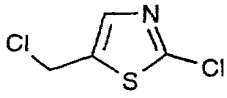
in which M^+ is as defined in claim 1, with an oxidizing agent, in the presence or absence of a base, and further reacting the compound thus obtainable, of the formula



IV,

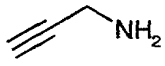
with or without isolating it, with a chlorinating agent.

62. A process according to claim 1 for the preparation of a compound of the formula



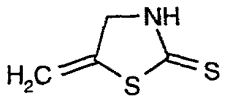
I,

which comprises reacting the compound of the formula



VII

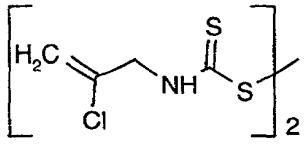
with carbon disulfide, in the presence or absence of a base, and further reacting the compound thus obtainable, of the formula



II,

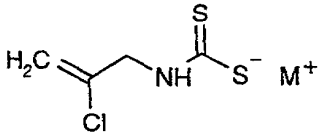
in free form or in salt form and with or without isolating it, with a chlorinating agent.

63. The compound of the formula



IV.

64. A process for the preparation of the compound according to claim 63, of the formula IV, which comprises reacting a compound of the formula

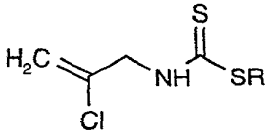


V,

in which M^+ is as defined in claim 1, with an oxidizing agent, in the presence or absence of a base.

65. The use of the compound according to claim 63, of the formula IV, in a process according to any one of claims 1, 26 to 36 and 61.

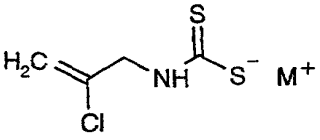
66. A compound of the formula



III,

in which R is as defined in claim 1.

67. A process for the preparation of a compound according to claim 66, of the formula III, which comprises reacting a compound of the formula



V,

in which M^+ is as defined in claim 1, with a compound of the formula RX, in which R is as defined in claim 1 for the formula III and X is a leaving group.

US Case PI/5 -20691/A

DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

☒ Original ☐ Supplemental ☐ Substitute

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

Process for the preparation of 2-chloro-5-chloromethyl-thiazole

the specification of which:

☐ is attached hereto.

☐ was filed on _____ (day/month/year) as Application No. _____

and, if this box (☐) contains an ✖

☐ was amended on _____ (day/month/year)

☒ was filed as Patent Cooperation Treaty international Application No.

PCT/EP 96/05564 on **12/12/1996** (day/month/year)

and, if this box (☐) contains an ✖

☐ entered the national stage in the United States and was accorded Application No.

_____

and, if this box (☐) contains an ✖

☐ was amended, subsequent to entry into the national stage, on _____ (day/month/year)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above and, if this application was filed as a Patent Cooperation Treaty international application, by any amendments made during the international stage (including any made under Patent Cooperation Treaty Rule 91, Article 19 and Article 34).

I acknowledge my duty to disclose all information which is known by me to be material to the patentability of this application as defined in 37 C.F.R. § 1.56.

I hereby claim the benefit under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and under 35 U.S.C. §365(a) of any Patent Cooperation Treaty international application(s) designating at least one country other than the United States listed below and have also listed below any foreign application(s) for patent or inventor's certificate and Patent Cooperation Treaty international application(s) designating at least one country other than the United States for the same subject matter and having a filing date before that of the application the priority of which is claimed for that subject matter:

COUNTRY/REGION (OR P.C.T.)	APPLICATION No.	FILING DATE (day/month/year)	PRIORITY CLAIMED	
Switzerland	**3636/95**	**21/12/1995**	☒ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No
			☐ Yes	☐ No

I hereby claim the benefit under 35 U.S.C. § 119 (e) of any United States provisional application(s) listed below:

APPLICATION NO.	FILING DATE (day/month/year)

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) listed below and under 35 U.S.C. §365(c) of any Patent Cooperation Treaty international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of 35 U.S.C. §112, I acknowledge my duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

United States Application No.	United States Filing Date (day/month/year)	Status (Pending, Abandoned or U.S. Patent No.)	International Application No.	and Filing Date

I hereby appoint the registered practitioners associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

If these brackets contain an X [X], I hereby authorize the registered practitioners associated with Customer No. 001095 and any others acting on my behalf to take any action relating to this application based on communications from the Patents and Trademarks Division of Novartis Services AG, Basle, Switzerland, or an affiliate thereof or a successor thereto, without direct communication from me.

Please address all communications to Michael W. Glynn, Novartis Corporation, Patent and Trademark Department, 564 Morris Avenue, Summit, NJ 07901-1027.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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Inventor's signature: Anthony Cornelius O'Sullivan Date: 10th June '98 (day/month/year)

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IMPORTANT: Before this declaration is signed, the patent application (the specification, the claims and this declaration) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.

2nd

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3rd

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5

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6-10

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